VERSION WITH MARKINGS TO SHOW CHANGES MADE

CLAIMS:

1. A multiparticulate bisoprolol formulation for once-daily oral administration, each particle comprising a core of bisoprolol or a pharmaceutically acceptable salt thereof surrounded by a polymeric coating, said polymeric coating being effective to achieve an initial lag of bisoprolol release *in vivo* of at least 4-6 hours following administration and thereafter maintaining therapeutic concentrations of bisoprolol for the remainder of the twenty-four hour period.

2. A multiparticulate bisoprolol formulation according to Claim 1, wherein the polymeric coating is effective to prevent quantifiable bisoprolol plasma concentrations *in vivo* for a period of at least 3-6 hours.

3. A multiparticulate bisoprolol formulation according to Claim 1 [or 2], which contains a pharmaceutically acceptable salt of bisoprolol.

4. A multiparticulate bisoprolol formulation according to Claim 3, wherein the salt is bisoprolol hemifumarate.

5. A multiparticulate bisoprolol formulation according to [any preceding claim] Claim 1, which has an *in vitro* dissolution profile which when measured in a U.S. Pharmacopoeia 2 Apparatus (Paddles) in phosphate buffer at pH 6.8 at 37°C and 50 rpm substantially corresponds to the following:

(a) from 0% to 10% of the total bisoprolol is released after 2 hours of measurement in said apparatus;

(b) from 0% to 50% of the total bisoprolol is released after 4 hours of measurement in said apparatus; and

(c) greater than 50% of the total bisoprolol is released after 10 hours of measurement in said apparatus.

6. A multiparticulate bisoprolol formulation according to [any preceding claim] Claim 1, which has an *in vitro* dissolution profile which when measured in a U.S. Pharmacopoeia 1 Apparatus (Baskets) at 37°C and 50 rpm in 0.01 N HCl for the first 2 hours followed by transfer to phosphate buffer at pH 6.8 for the remainder of the measuring period substantially corresponds to the following:

(a) from 0% to 10% of the total bisoprolol is released after 2 hours of measurement in said apparatus;

(b) less than 50% of the total bisoprolol is released after 4 hours of measurement in said apparatus; and

(c) greater than 20% of the total bisoprolol is released after 10 hours of measurement in said apparatus.

7. A multiparticulate bisoprolol formulation according to [any preceding claim] Claim 1, wherein a sealant or barrier layer is applied to the core prior to the application of the polymeric coating.

8. A multiparticulate bisoprolol formulation according to Claim 7, wherein the sealant or barrier is selected from hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxypropyl ethylcellulose and xanthan gum.

9. A multiparticulate bisoprolol formulation according to [any preceding claim] Claim 1, wherein the bisoprolol active ingredient is applied to a non-pareil seed having an average diameter in the range of 0.4-1.1mm.

10. A multiparticulate bisoprolol formulation according to [any preceding claim] Claim 1, wherein the polymeric coating contains a major proportion of a pharmaceutically acceptable film-forming polymer which forms an insoluble film of low permeability.

11. A multiparticulate bisoprolol formulation according to [any preceding claim] Claim 1, wherein the polymeric coating contains a minor proportion of a pharmaceutically acceptable film-forming polymer which forms an insoluble film of high permeability.

12. A multiparticulate bisoprolol formulation according to Claim 10 [or 11], wherein the or each polymer is a methacrylic acid co-polymer.

13. A multiparticulate bisoprolol formulation according to Claim 10 [or 11], wherein the or each polymer is an ammonio methacrylate co-polymer.

14. A multiparticulate bisoprolol formulation according to Claim 12 [or 13], wherein a mixture of said polymers is used.

15. A multiparticulate bisoprolol formulation according to [any preceding claim] Claim 1, wherein the polymeric coating includes one or more soluble excipients so as to increase the permeability of the coating.

16. A multiparticulate bisoprolol formulation according to Claim 15, wherein the or each soluble excipient is selected from a soluble polymer, a surfactant, an alkali metal salt, an organic acid, a sugar and a sugar alcohol.

17. A multiparticulate bisoprolol formulation according to Claim 15 [or 16], wherein the soluble excipient is selected from polyvinyl pyrrolidone, polyethylene glycol and mannitol.

18. A multiparticulate bisoprolol formulation according to [any one of Claims 15-17] Claim 15, wherein the soluble excipient is used in an amount of from 1% to 10% by weight, based on the total dry weight of the polymer.

19. A multiparticulate bisoprolol formulation according to [any preceding claim] Claim 1, wherein the polymeric coating includes one or

more auxiliary agents selected from a filler, a plasticiser and an anti-foaming agent.

20. A multiparticulate bisoprolol formulation according to [any preceding claim] Claim 1, wherein the coating polymer is coated to 10% to 100% weight gain on the core.

21. A multiparticulate bisoprolol formulation according to [any preceding claim] Claim 1, wherein the coating polymer is coated to 25% to 70% weight gain on the core.

22. A multiparticulate bisoprolol formulation according to [any preceding claim] Claim 1, wherein a sealant or barrier layer is applied to the polymeric coating.

23. A multiparticulate bisoprolol formulation according to Claim 22, wherein the sealant or barrier is selected from hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxypropyl ethylcellulose and xanthan gum.

24. An oral dosage form containing a multiparticulate bisoprolol formulation according to [any one of Claims 1-23] Claim 1, which is in the form of caplets, capsules, particles for suspension prior to dosing, sachets or tablets.

25. An oral dosage form according to Claim 24, which is in the form of tablets selected from disintegrating tablets, fast dissolving tablets, effervescent tablets, fast melt tablets and mini-tablets.

[26. A multiparticulate bisoprolol formulation according to Claim 1, substantially as hereinbefore described and exemplified.]

[27. An oral dosage form according to Claim 24, substantially as hereinbefore described.]

28. A multiparticulate bisoprolol formulation according to Claim 11, wherein the or each polymer is a methacrylic acid co-polymer.

29. A multiparticulate bisoprolol formulation according to Claim 11, wherein the or each polymer is an ammonio methacrylate co-polymer.

30. A multiparticulate bisoprolol formulation according to Claim 13, wherein a mixture of said polymers is used.

PREVIOUS VERSION

CLAIMS: -

1. A multiparticulate bisoprolol formulation for once-daily oral administration, each particle comprising a core of bisoprolol or a pharmaceutically acceptable salt thereof surrounded by a polymeric coating, said polymeric coating being effective to achieve an initial lag of bisoprolol release *in vivo* of at least 4-6 hours following administration and thereafter maintaining therapeutic concentrations of bisoprolol for the remainder of the twenty-four hour period.

2. A multiparticulate bisoprolol formulation according to Claim 1, wherein the polymeric coating is effective to prevent quantifiable bisoprolol plasma concentrations *in vivo* for a period of at least 3-6 hours.

3. A multiparticulate bisoprolol formulation according to Claim 1 or 2, which contains a pharmaceutically acceptable salt of bisoprolol.

4. A multiparticulate bisoprolol formulation according to Claim 3, wherein the salt is bisoprolol hemifumarate.

5. A multiparticulate bisoprolol formulation according to any preceding claim, which has an *in vitro* dissolution profile which when measured in a U.S. Pharmacopoeia 2 Apparatus (Paddles) in phosphate buffer at pH 6.8 at 37°C and 50 rpm substantially corresponds to the following:

(a) from 0% to 10% of the total bisoprolol is released after 2 hours of measurement in said apparatus;

(b) from 0% to 50% of the total bisoprolol is released after 4 hours of measurement in said apparatus; and

(c) greater than 50% of the total bisoprolol is released after 10 hours of measurement in said apparatus.

6. A multiparticulate bisoprolol formulation according to any preceding claim, which has an *in vitro* dissolution profile which when measured in a U.S. Pharmacopoeia 1 Apparatus (Baskets) at 37°C and 50 rpm in 0.01 N HCl for the first 2 hours followed by transfer to phosphate buffer at pH 6.8 for the remainder of the measuring period substantially corresponds to the following:

(a) from 0% to 10% of the total bisoprolol is released after 2 hours of measurement in said apparatus;

(b) less than 50% of the total bisoprolol is released after 4 hours of measurement in said apparatus; and

(c) greater than 20% of the total bisoprolol is released after 10 hours of measurement in said apparatus.

7. A multiparticulate bisoprolol formulation according to any preceding claim, wherein a sealant or barrier layer is applied to the core prior to the application of the polymeric coating.

8. A multiparticulate bisoprolol formulation according to Claim 7, wherein the sealant or barrier is selected from hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxypropyl ethylcellulose and xanthan gum.

9. A multiparticulate bisoprolol formulation according to any preceding claim, wherein the bisoprolol active ingredient is applied to a non-pareil seed having an average diameter in the range of 0.4-1.1mm.

10. A multiparticulate bisoprolol formulation according to any preceding claim, wherein the polymeric coating contains a major proportion of a pharmaceutically acceptable film-forming polymer which forms an insoluble film of low permeability.

11. A multiparticulate bisoprolol formulation according to any preceding claim, wherein the polymeric coating contains a minor proportion of a pharmaceutically acceptable film-forming polymer which forms an insoluble film of high permeability.

12. A multiparticulate bisoprolol formulation according to Claim 10 or 11, wherein the or each polymer is a methacrylic acid co-polymer.

13. A multiparticulate bisoprolol formulation according to Claim 10 or 11, wherein the or each polymer is an ammonio methacrylate co-polymer.

14. A multiparticulate bisoprolol formulation according to Claim 12 or 13, wherein a mixture of said polymers is used.

15. A multiparticulate bisoprolol formulation according to any preceding claim, wherein the polymeric coating includes one or more soluble excipients so as to increase the permeability of the coating.

16. A multiparticulate bisoprolol formulation according to Claim 15, wherein the or each soluble excipient is selected from a soluble polymer, a surfactant, an alkali metal salt, an organic acid, a sugar and a sugar alcohol.

17. A multiparticulate bisoprolol formulation according to Claim 15 or 16, wherein the soluble excipient is selected from polyvinyl pyrrolidone, polyethylene glycol and mannitol.

18. A multiparticulate bisoprolol formulation according to any one of Claims 15-17, wherein the soluble excipient is used in an amount of from 1% to 10% by weight, based on the total dry weight of the polymer.

19. A multiparticulate bisoprolol formulation according to any preceding claim, wherein the polymeric coating includes one or more

auxiliary agents selected from a filler, a plasticiser and an anti-foaming agent.

20. A multiparticulate bisoprolol formulation according to any preceding claim, wherein the coating polymer is coated to 10% to 100% weight gain on the core.

21. A multiparticulate bisoprolol formulation according to any preceding claim, wherein the coating polymer is coated to 25% to 70% weight gain on the core.

22. A multiparticulate bisoprolol formulation according to any preceding claim, wherein a sealant or barrier layer is applied to the polymeric coating.

23. A multiparticulate bisoprolol formulation according to Claim 22, wherein the sealant or barrier is selected from hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxypropyl ethylcellulose and xanthan gum.

24. An oral dosage form containing a multiparticulate bisoprolol formulation according to any one of Claims 1-23, which is in the form of caplets, capsules, particles for suspension prior to dosing, sachets or tablets.

25. An oral dosage form according to Claim 24, which is in the form of tablets selected from disintegrating tablets, fast dissolving tablets, effervescent tablets, fast melt tablets and mini-tablets.

26. A multiparticulate bisoprolol formulation according to Claim 1, substantially as hereinbefore described and exemplified.

27. An oral dosage form according to Claim 24, substantially as hereinbefore described.